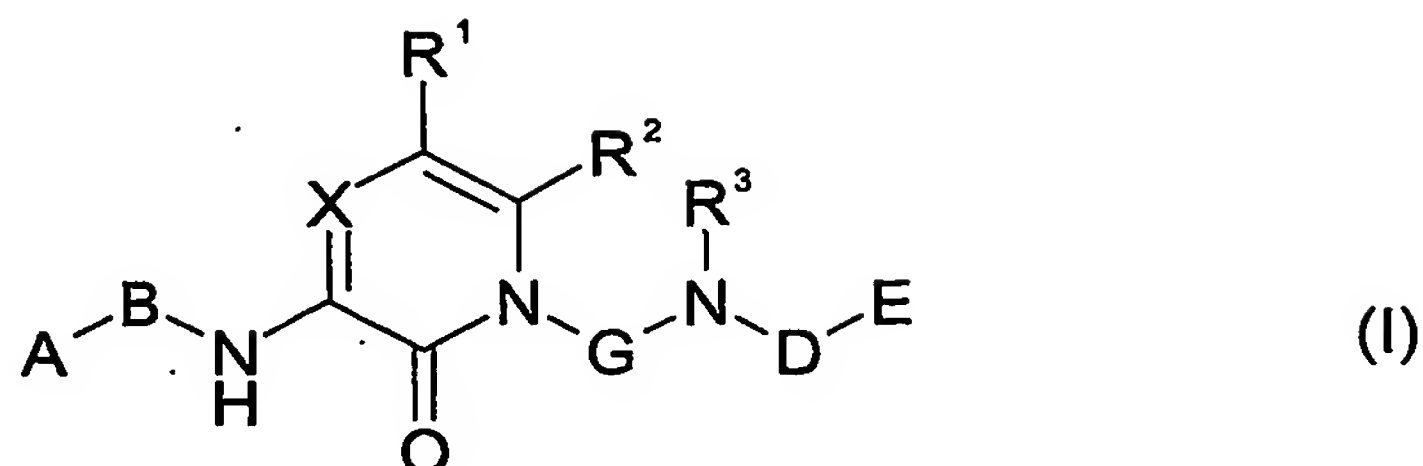


Claims

1. A compound of formula (I)



or a pharmaceutically acceptable salt thereof, wherein:

R¹ is hydrogen;
 halogen; or
 C₁₋₄ alkyl, optionally substituted with one or more fluoro;

R² is hydrogen;
 halogen;
 C₁₋₆ alkyl, optionally substituted with one or more fluoro;
 C₃₋₆ cycloalkyl; or
 O-C₁₋₄ alkyl;

R³ is hydrogen;
 C₁₋₄ alkyl; or
 C₃₋₆ cycloalkyl;

A is A¹, wherein A¹ is selected from the group consisting of:
 phenyl;
 naphthyl;
 heterocycle containing up to 4 heteroatoms, which are the same or different and
 selected from the group consisting of -O-, -S-, -S(O)-, -S(O₂)-, -N=,
 -N(O)= and -N(R⁴)-; and
 heterobicycles containing up to 6 heteroatoms, which are the same or different

and selected from the group consisting of -O-, -S-, -S(O)-, -S(O₂)-, -N=, -N(O)= and -N(R⁴)-;

wherein A¹ is optionally substituted with one or independently from each other more of

A²;

A³;

halogen;

-N(R⁵R⁶);

-OH;

=O, where the ring is at least partially saturated;

C₃₋₆ cycloalkyl;

-COOR⁷; or

-CONR⁸R⁹;

-S(O)₂NR^{8a}R^{9a}

and wherein R⁴, R⁵, R⁶ are independently selected from the group consisting of R^{7a}, -C(O)-R^{7a}, -C(O)O-R^{7a}, -C(O)NR^{7a}R^{7b}, -S(O)₂NR^{7a}R^{7b}, and S(O)₂-R^{7a};

and wherein R⁷, R^{7a}, R^{7b}, R⁸, R^{8a}, R⁹, R^{9a} are independently hydrogen or C₁₋₄ alkyl, wherein each C₁₋₄ alkyl is optionally substituted with one or more substituents independently selected from the group consisting of -COOH; -OH; -NH₂; -NH-C₁₋₄ alkyl; -N(C₁₋₄ alkyl)₂; and C₃₋₆ cycloalkyl;

Optionally R⁴ is a bond to directly attach A to B;

A² is selected from the group consisting of A⁴, -O-A⁴ and -N(R¹⁰)-A⁴,

wherein A⁴ is phenyl or a heterocycle containing up to 4 heteroatoms, which are the same or different and selected from the group consisting of -O-, -S-, -S(O)-, -S(O₂)-, -N=, -N(O)= and -N(R¹¹)-; wherein A⁴ is optionally substituted with one or independently from each other more of

fluoro;

chloro;

-N(R¹²R¹³)

C₁₋₄ alkyl or -O-C₁₋₄ alkyl, both optionally substituted with one or independently from each other more of fluoro or -N(R¹⁴R¹⁵);

and wherein R¹⁰, R¹², R¹³, R¹⁴, R¹⁵ are independently hydrogen or C₁₋₄ alkyl;

and wherein R¹¹ is selected from the group consisting of hydrogen, C₁₋₄ alkyl

and -C(O)-C₁₋₄ alkyl;

A³ is selected from the group consisting of C₁₋₆ alkyl, -O-C₁₋₆ alkyl and -N(R¹⁶)-C₁₋₆ alkyl, wherein the C₁₋₆ alkyl group is optionally substituted with one or independently from each other more of

fluoro;

-N(R¹⁷R¹⁸);

A⁵;

and/or A³ is optionally interrupted with one or more oxygen;

and wherein R¹⁶, R¹⁷, R¹⁸ are independently hydrogen or C₁₋₄alkyl;

A⁵ is phenyl or a heterocycle containing up to 4 heteroatoms, which are the same or different and selected from the group consisting of -O-, -S-, -S(O)-, -S(O₂)-, -N=, -N(O)= and -N(R¹⁹)-; wherein A⁵ is optionally substituted with one or independently from each other more of

fluoro;

chloro;

-N(R²⁰R²¹)

C₁₋₄ alkyl or -O-C₁₋₄ alkyl, both optionally substituted with one or independently from each other more of fluoro or -N(R²²R²³);

and wherein R¹⁹ is selected from the group consisting of hydrogen, C₁₋₄ alkyl and -C(O)-C₁₋₄ alkyl;

and wherein R²⁰, R²¹, R²², R²³ are independently hydrogen or C₁₋₄ alkyl;

B is selected from the group consisting of -Y-Z-; -Y-Z-C(O)-; -Y-Z-O-C(O)-; -Y-Z-S(O)₂-; and -Y-Z-NH-C(O)- wherein

Y is a bond, -O-, -S-, -N(R²⁴)-, -N(R²⁵)-C(O)-, -C(O)-N(R²⁶)-, or -C(O)-;

Z is C₁₋₆ alkyl,

optionally interrupted with oxygen, sulfur or -N(R²⁷)-

and/or optionally substituted with one or independently from each other more of

halogen;

C₃₋₆ cycloalkyl;

-COOR²⁸;

-CON(R²⁹R³⁰)

and/or optionally one chain carbon forms part of a C₃₋₆ cycloalkyl;
 and wherein R²⁴, R²⁵, R²⁶, R²⁷, R²⁸, R²⁹, R³⁰ are independently
 hydrogen; or
 C₁₋₄ alkyl, optionally substituted with -COOR³¹ or -CON(R³²R³³)
 wherein R³¹, R³², R³³ are independently hydrogen or
 C₁₋₄ alkyl;

X is =C(R³⁴)- or =N-, wherein R³⁴ is
 hydrogen;
 C₁₋₆ alkyl, optionally substituted with one or more fluoro; or
 -S(O)₂R³⁵, wherein R³⁵ is selected from the group consisting of X¹, C₁₋₆ alkyl,
 and -C₁₋₆ alkyl-X¹; wherein R³⁵ is optionally substituted with one or
 independently from each other more of
 fluoro;
 chloro;
 C₁₋₄ alkyl; or
 -O-C₁₋₄ alkyl;

X¹ is phenyl or heterocycle containing up to 4 heteroatoms, which are the same or
 different and selected from the group consisting of -O-, -S-, -S(O)-, -S(O)₂-, -N=, -N(O)=
 and -N(R³⁶)-; and wherein R³⁶ is selected from the group consisting of hydrogen,
 C₁₋₄ alkyl and -C(O)-C₁₋₄ alkyl;

G is -CH(R³⁷)-C(R³⁸R³⁹)-;
 -CH(R³⁷)-C(R³⁸R³⁹)-C(R⁴⁰R⁴¹)-;
 wherein R³⁷, R³⁸, R³⁹, R⁴⁰, R⁴¹ are independently
 hydrogen;
 C₁₋₄ alkyl, optionally substituted with one or more fluoro;
 C₃₋₆ cycloalkyl, optionally substituted with one or more fluoro;
 or R³⁸ and R³⁹ or R⁴⁰ and R⁴¹ form together C₃₋₆ cycloalkyl, optionally
 substituted with one or more fluoro, -OH, C₁₋₄ alkyl;
 or R³⁷ and R³⁸ or R³⁸ and R⁴⁰ form together C₃₋₆ cycloalkyl, optionally
 substituted with one or more fluoro, -OH, C₁₋₄ alkyl;

D is C₁₋₆ alkyl,

optionally interrupted with oxygen, sulfur or $-N(R^{42})-$
 and/or optionally substituted with halogen, C_{3-6} cycloalkyl;
 and/or optionally one chain carbon or two vicinal carbons form part of a C_{3-6}
 cycloalkyl, wherein R^{42} is selected from the group consisting of hydrogen, C_{1-4}
 alkyl, C_{3-6} cycloalkyl and $-C(O)-C_{1-4}$ alkyl;

E is E^1 , wherein E^1 is selected from the group consisting of
 phenyl;
 naphthyl;
 heterocycle containing up to 4 heteroatoms, which are the same or different and
 selected from the group consisting of $-O-$, $-S-$, $-S(O)-$, $-S(O_2)-$, $-N=$,
 $-N(O)=$ and $-N(R^{43})-$; and
 heterobicycle containing up to 6 heteroatoms, which are the same or different
 and selected from the group consisting of $-O-$, $-S-$, $-S(O)-$, $-S(O_2)-$, $-N=$,
 $-N(O)=$ and $-N(R^{44})-$;
 wherein E^1 is optionally substituted with one or independently from each other
 more of

E^2 ;

E^3 ;

halogen;

$-N(R^{45}R^{46})$;

$-OH$;

$=O$, where the ring is at least partially saturated;

C_{3-6} cycloalkyl;

$-COOR^{47}$; or

$-CONR^{48}R^{49}$;

$-S(O)_2NR^{48a}R^{49a}$;

and wherein R^{43} , R^{44} , R^{45} , R^{46} are independently selected from the group
 consisting of hydrogen;

C_{1-4} alkyl optionally substituted with $-OH$;

and $-C(O)-C_{1-4}$ alkyl optionally substituted with $-OH$;

and wherein R^{47} , R^{48} , R^{48a} , R^{49} , R^{49a} are independently hydrogen or C_{1-4} alkyl,
 optionally substituted with $-OH$;

E^2 is selected from the group consisting of E^4 , $-C(O)-E^4$, $-O-E^4$ and $-N(R^{50})-E^4$,

wherein E^4 is phenyl or heterocycle containing up to 4 heteroatoms, which are the same or different and selected from the group consisting of -O-, -S-, -S(O)-, -S(O₂)-, -N=, -N(O)= and -N(R⁵¹)-; wherein E^4 is optionally substituted with one or independently from each other more of

fluoro;

chloro;

cyano;

=O, where the ring is at least partially saturated;

-N(R⁵²R⁵³);

C₁₋₄ alkyl; or

-O-C₁₋₄ alkyl;

and wherein R⁵⁰, R⁵², R⁵³ are independently hydrogen or C₁₋₄ alkyl, optionally substituted with -OH;

and wherein R⁵¹ is selected from the group consisting of

hydrogen;

C₁₋₄ alkyl, optionally substituted with -OH; and

-C(O)-C₁₋₄ alkyl, optionally substituted with -OH;

E^3 is selected from the group consisting of C₁₋₆ alkyl, -O-C₁₋₆ alkyl; -N(R⁵⁴)-C₁₋₆ alkyl, wherein E^3 is optionally substituted with one or independently from each other more of

fluoro;

-N(R⁵⁵R⁵⁶);

E^5 ;

and/or E^3 is optionally interrupted with one or more oxygen;

and wherein R⁵⁴, R⁵⁵, R⁵⁶ are independently hydrogen or C₁₋₄alkyl, optionally substituted with -OH;

E^5 is phenyl or heterocycle containing up to 4 heteroatoms, which are the same or different and selected from the group consisting of -O-, -S-, -S(O)-, -S(O₂)-, -N=, -N(O)= and -N(R⁵⁷)-; wherein E^5 is optionally substituted with one or independently from each other more of

fluoro;

chloro;

cyano;

=O, where the ring is at least partially saturated;

-N(R⁵⁸R⁵⁹);

C₁₋₄ alkyl or

-O-C₁₋₄ alkyl;

and wherein R⁵⁷ is independently selected from the group consisting of hydrogen;

C₁₋₄ alkyl, optionally substituted with -OH; and

-C(O)-C₁₋₄ alkyl, optionally substituted with -OH;

and wherein R⁵⁸, R⁵⁹ are independently hydrogen or C₁₋₄ alkyl, optionally substituted with -OH.

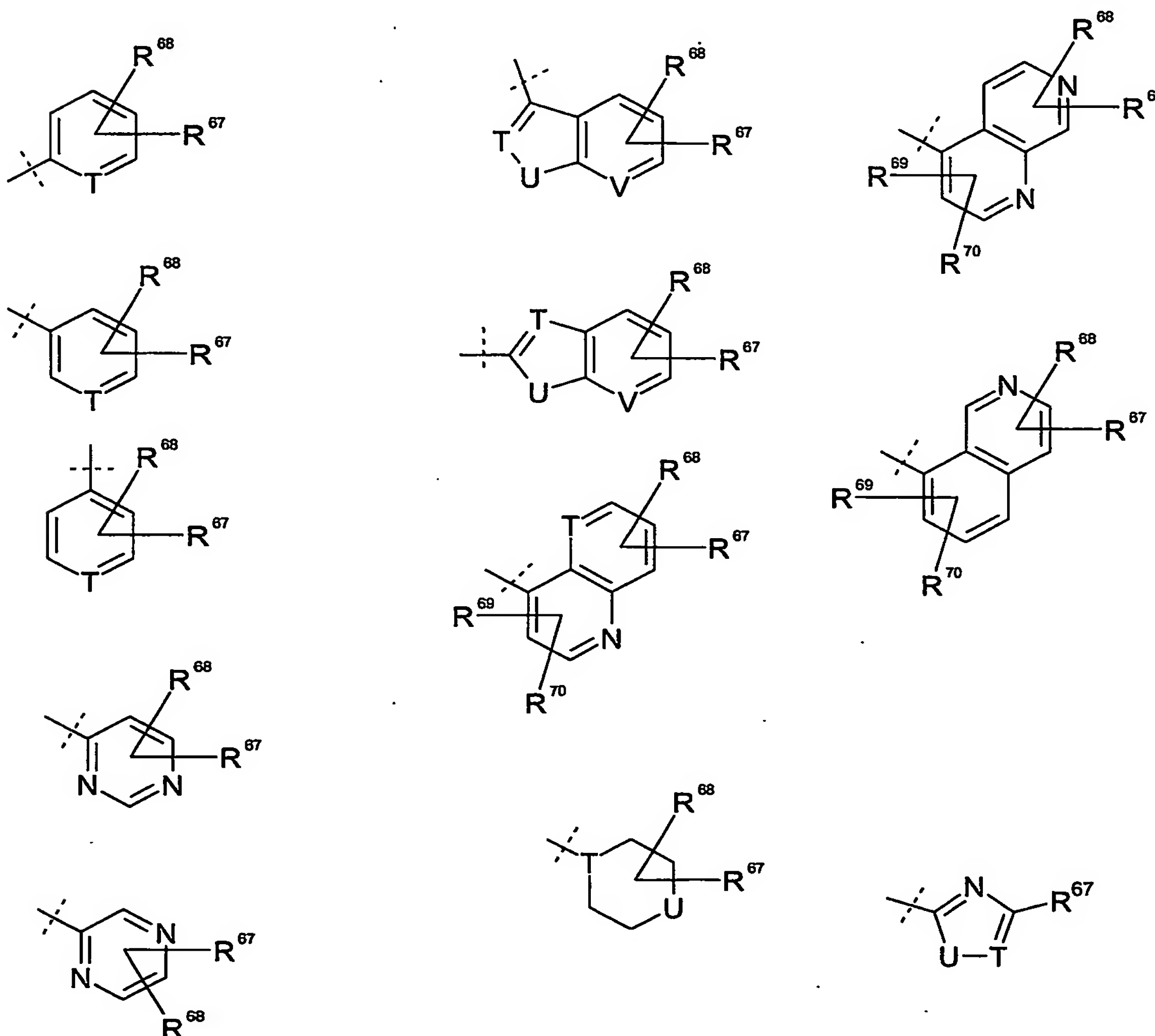
2. A compound according to claim 1, wherein R¹ is hydrogen.
3. A compound according to claim 1 or 2, wherein R² is hydrogen, chloro, -CH₃, -CH₂-CH₃, -CH₂-CH₂-CH₃, -CH₂-CH₂-CH₂-CH₃, -CH₂F, -CHF₂ or -CN.
4. A compound according to any one of the preceding claims, wherein R³ is hydrogen.
5. A compound according to any one of the preceding claims, wherein A¹ is phenyl or heterocycle containing up to 4 heteroatoms, which are the same or different and selected from the group consisting of -O-, -S-, -S(O)-, -S(O)₂-, -N=, -N(O)= and -N(R⁴)-, wherein R⁴ has the meaning as indicated in claim 1.
6. A compound according to claim 5, wherein A¹ is selected from the group consisting of phenyl, pyridine, pyridine-N oxide, piperidine, morpholine, and pyrrolidine.
7. A compound according to any of the preceding claims, wherein R⁴ is a bond, -COOC₁₋₄ alkyl, methyl, ethyl, 2-hydroxyethyl, -COOH, -CH₂-COOH, -CH₂-COO-C₁₋₄ alkyl or cyclopropylmethyl and wherein A¹ is optionally substituted with up to 4 F.
8. A compound according to any one of the preceding claims, wherein B is -Y-Z-.
9. A compound according to any one of the preceding claims, wherein Y is a bond, -O-, -NH-, -S(O)₂- or -C(O)-.

10. A compound according to any one of the preceding claims, wherein Z is -
C(R⁶⁰R⁶¹)- or -C(R⁶⁰R⁶¹)-C(R⁶²R⁶³)-, wherein
R⁶⁰, R⁶¹, R⁶², R⁶³ are independently hydrogen, -C(O)NH₂, -COOH, -CH₂-COOH,
-CH₂-C(O)NH₂, fluoro, methyl, cyclopropyl or
R⁶⁰ and R⁶¹ form a cyclopropyl ring or
R⁶² and R⁶³ form a cyclopropyl ring or
R⁶⁰ and R⁶² form a cyclopropyl or cyclobutyl ring.
11. A compound according to claim 10, wherein R⁶⁰, R⁶¹, R⁶², R⁶³ are independently
hydrogen, fluoro or -C(O)NH₂.
12. A compound according to any one of the preceding claims, wherein X is =N-.
13. A compound according to any of the preceding claims, wherein G is
-CH(R⁶⁴)-C(R⁶⁵R⁶⁶)-; wherein R⁶⁴, R⁶⁵, R⁶⁶ are independently hydrogen, F, methyl,
-CH₂F, -CHF₂, CF₃ or cyclopropyl or R⁶⁵, R⁶⁶ form together cyclopropyl.
14. a compound according to any one of the preceding claims, wherein G is -CH₂-CH₂-.
15. A compound according to any one of the preceding claims, wherein D is -CH₂-, -
CF₂-, -CH(CH₃)-, -C(CH₃)₂- or D¹-D², where D¹ and D² are independently -CH₂-, -
CF₂-, -CH(CH₃)- or -C(CH₃)₂- and wherein D² is optionally -CH₂-NH-.
16. A compound according to claim 15, wherein D is -CH₂-, -CH(CH₃)-, -CH₂-CH₂-, -
CH₂-CF₂ or -CH₂-CH₂-NH-.
17. A compound according to any one of the preceding claims, wherein -E is selected
from the group consisting of phenyl; heterocycle containing up to three
heteroatoms, which are the same or different and selected from the group
consisting of -O-, -N=, -N(O)- and -NH-; and heterobicycle containing up to three
heteroatoms, which are the same or different and selected from the group
consisting of -O-, -N=, and -NH-; and wherein E is optionally substituted with up to
two substituents which are the same or different and selected from the group
consisting of CN, F, Cl, C₁₋₄ alkyl, OH, O-C₁₋₄ alkyl, NH₂, NH-C₁₋₄ alkyl, N(C₁₋₄
alkyl)₂, C(O)NH₂, C(O)NH-C₁₋₄ alkyl, and C(O)N(C₁₋₄ alkyl)₂, wherein each C₁₋₄ alkyl

is optionally substituted with one or more substituents independently selected from OH and F.

18. A compound according to claim 17, wherein -E is phenyl, pyridine, benzimidazole, indazole, quinoline, isoquinoline, pyridine-(N)-oxide, benzothiophene, indole, azaindole, benzofuran, benzisoxazole, benzoxazole, benzothiazole.

19. A compound according to any one of the preceding claims, wherein -E is selected from the group consisting of



wherein

T and V are independently =CH-, =CR⁷¹-, =N- or =N(O)-;

U is -NH-, -NR⁷²-, -O-, or -S-, wherein

R⁶⁷, R⁶⁸, R⁶⁹, R⁷⁰, R⁷¹ are independently selected from the group consisting of

hydrogen;

C₃₋₆ cycloalkyl;

E⁶;

E⁷;

halogen;

-N(R⁷³R⁷⁴);

-OH; and

-COOR⁷⁵ or -C(O)NR⁷⁶R⁷⁷;

and wherein R⁷², R⁷³, R⁷⁴, R⁷⁵, R⁷⁶, R⁷⁷ are independently

hydrogen;

C₁₋₄ alkyl; or

-C(O)-C₁₋₄ alkyl;

E⁶ is selected from the group consisting of C₁₋₆ alkyl; -O-C₁₋₆ alkyl; and -N(R⁷⁸)-C₁₋₆ alkyl, wherein the C₁₋₆ alkyl group is optionally substituted with one or more of

halogen;

-N(R⁷⁹R⁸⁰);

phenyl, optionally substituted with chloro;

heterocycle containing up to 4 heteroatoms, which are the same or different and selected from the group consisting of -O-, -S-, -S(O)-, -S(O₂)-, -N=, -N(O)= and -N(R⁸¹)-, optionally substituted with chloro;

and/or E⁶ is optionally interrupted by one or more of oxygen;

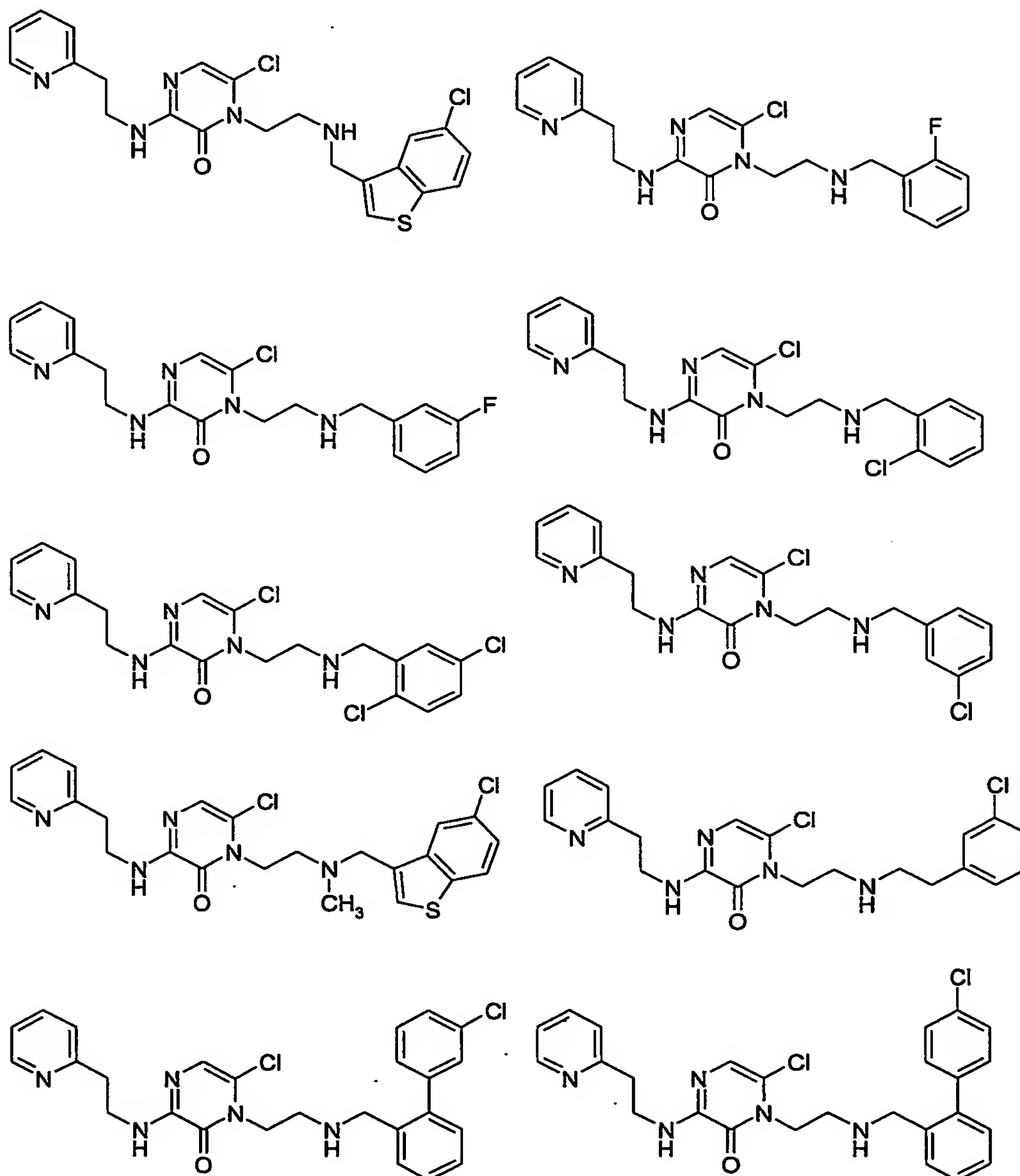
and wherein R⁷⁸, R⁷⁹, R⁸⁰, R⁸¹ are independently hydrogen, C₁₋₄alkyl;

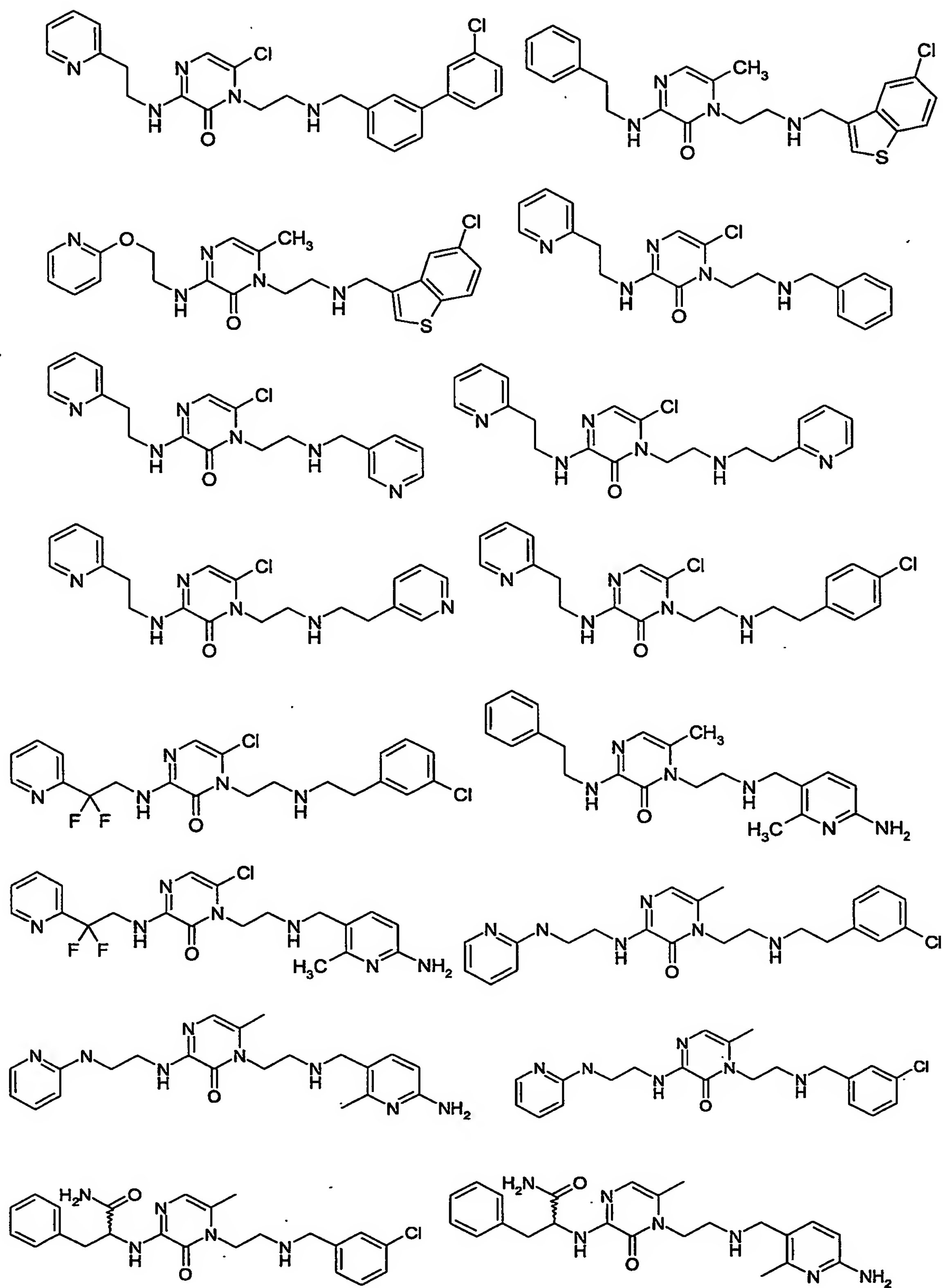
E⁷ is selected from the group consisting of E⁸; -O-E⁸; -N(R⁸²)-E⁸; and -C(O)-E⁸, wherein E⁸ is phenyl or heterocycle containing up to 4 heteroatoms, which are the same or different and selected from the group consisting of -O-, -S-, -S(O)-, -S(O₂)-, -N=, -N(O)= and -N(R⁸³)-; and wherein E⁸ is optionally substituted with chloro or -N(R⁸⁴R⁸⁵);

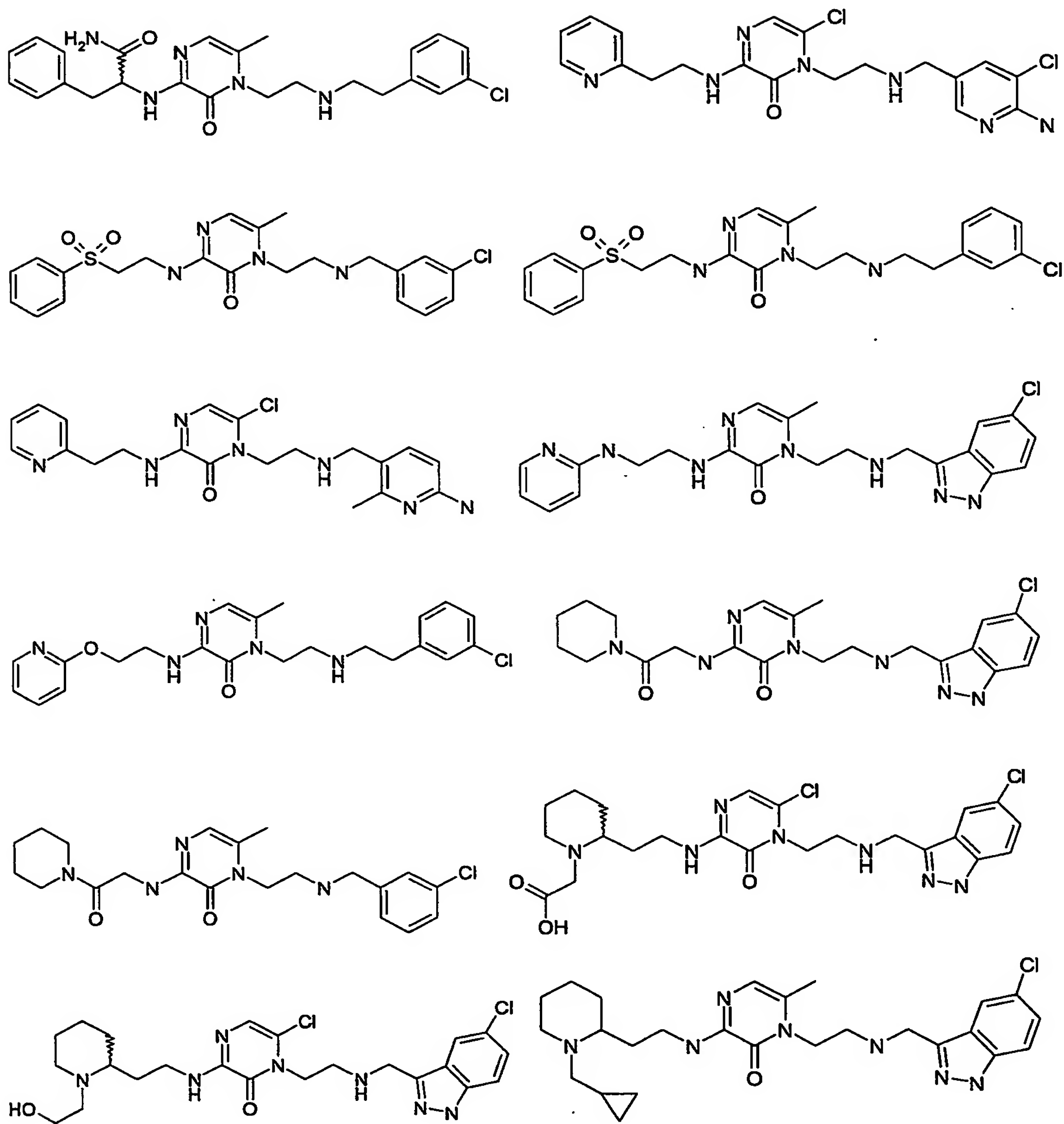
and wherein R⁸², R⁸³, R⁸⁴, R⁸⁵ are independently hydrogen or C₁₋₄ alkyl.

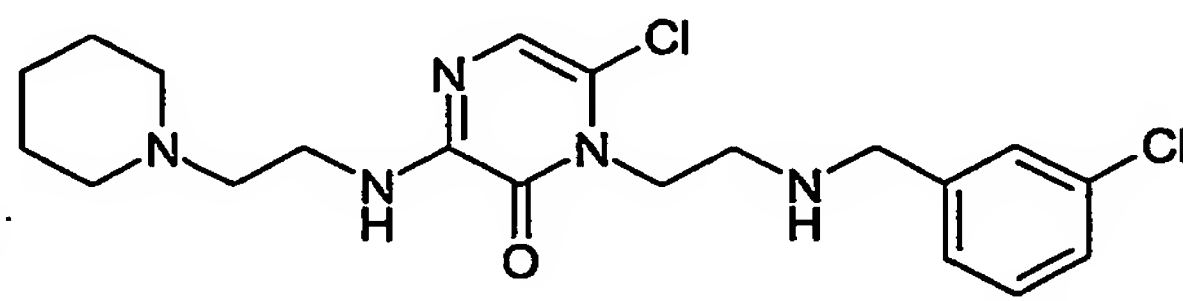
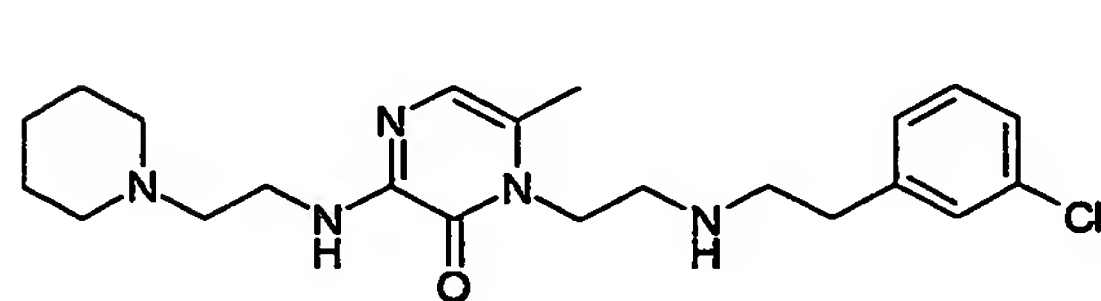
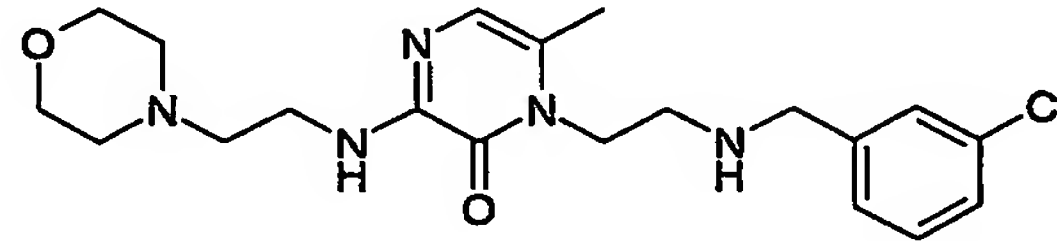
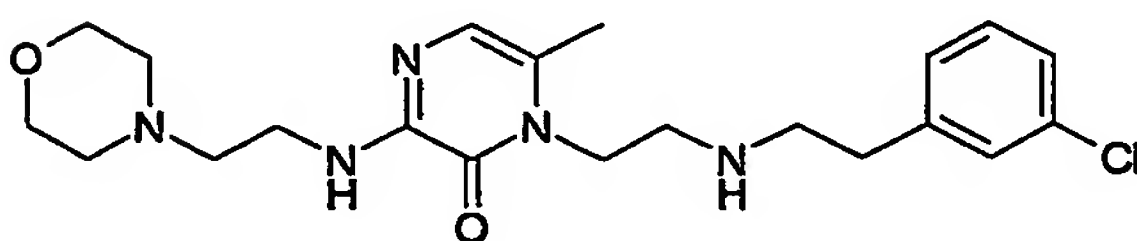
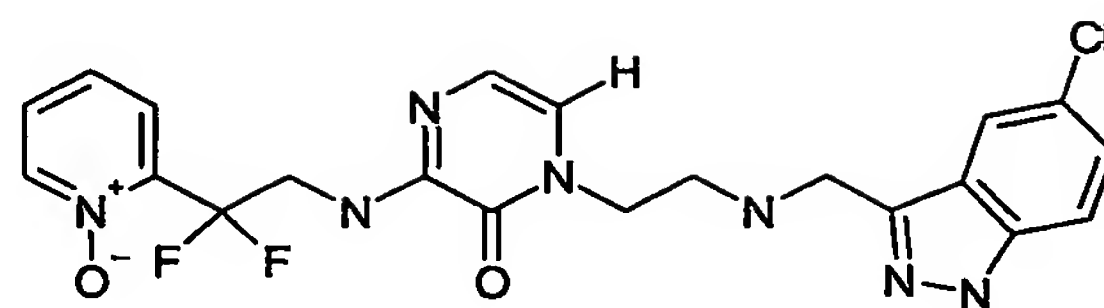
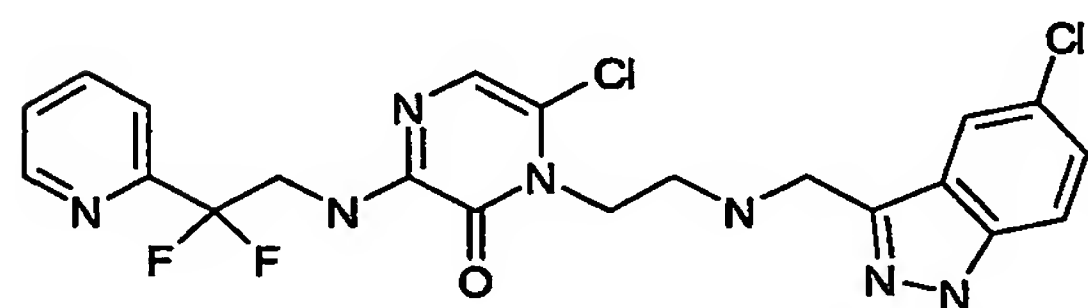
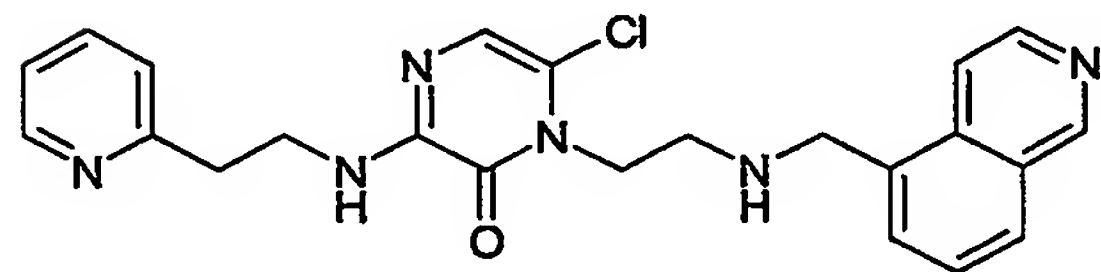
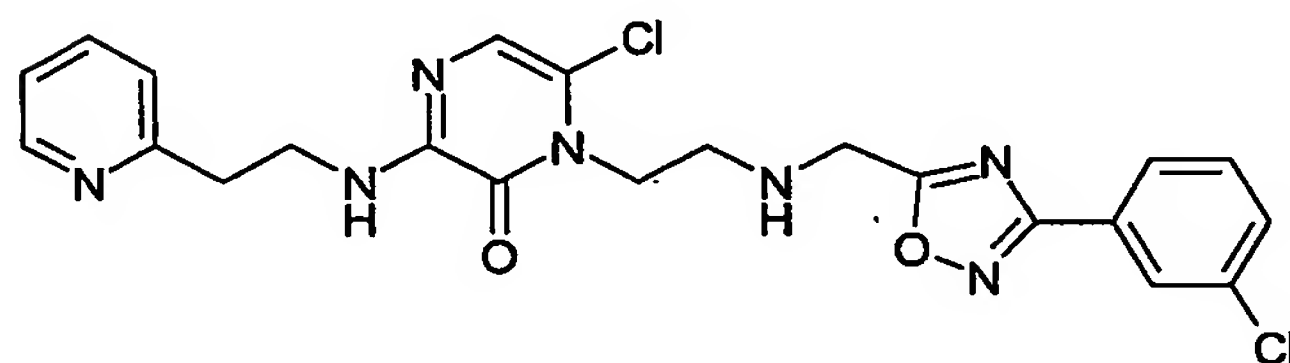
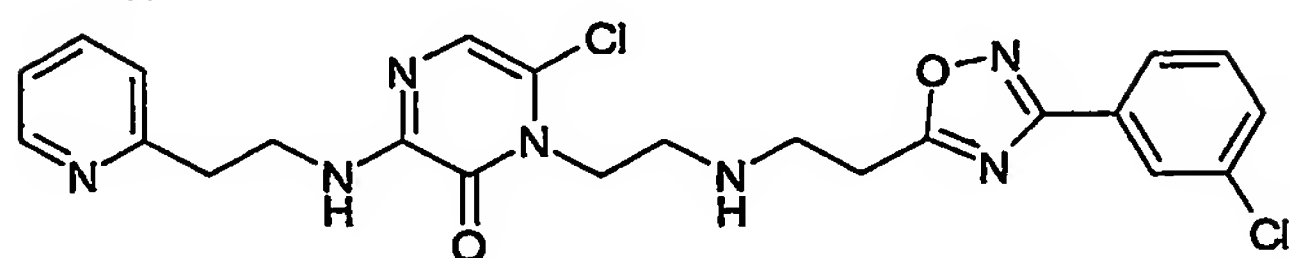
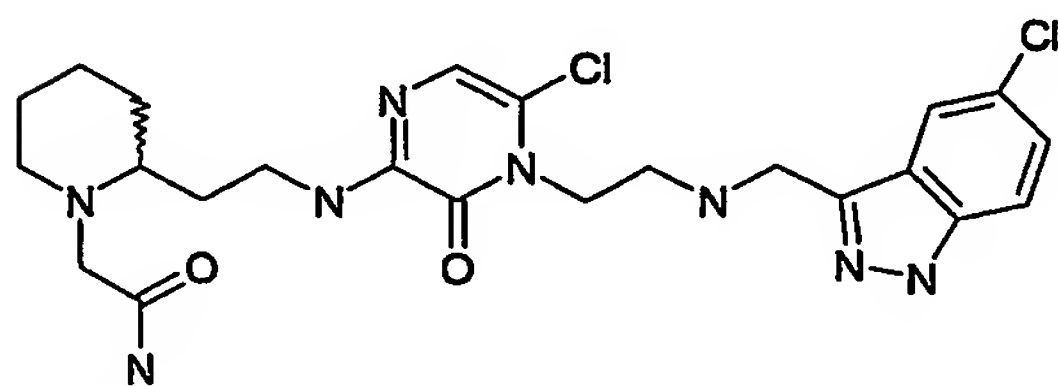
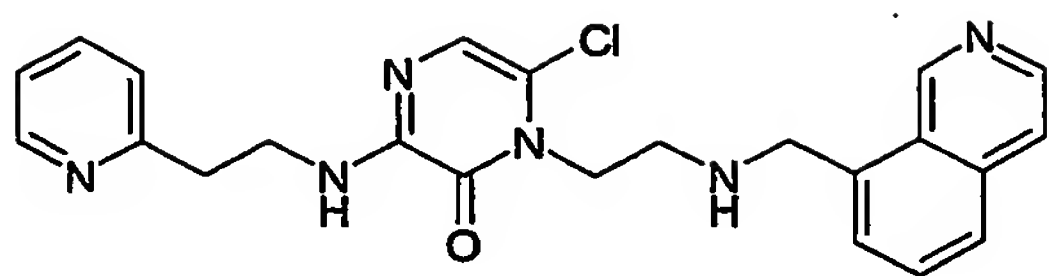
20. A compound according to claim 19, wherein R^{67} , R^{68} , R^{69} , R^{70} , R^{71} are independently selected from the group consisting of hydrogen, fluoro, chloro, cyano, phenyl, chlorophenyl, methyl, methoxy, amino, monomethyl amino, dimethyl amino, pyrrolyl, diazoly, triazolyl, and tetrazolyl.

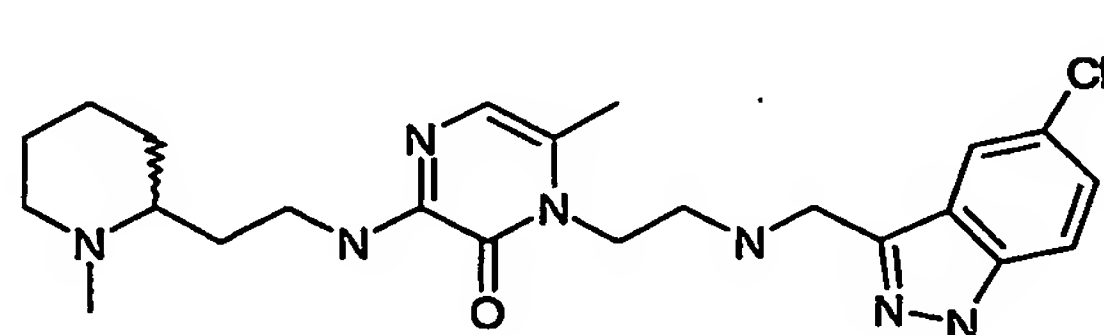
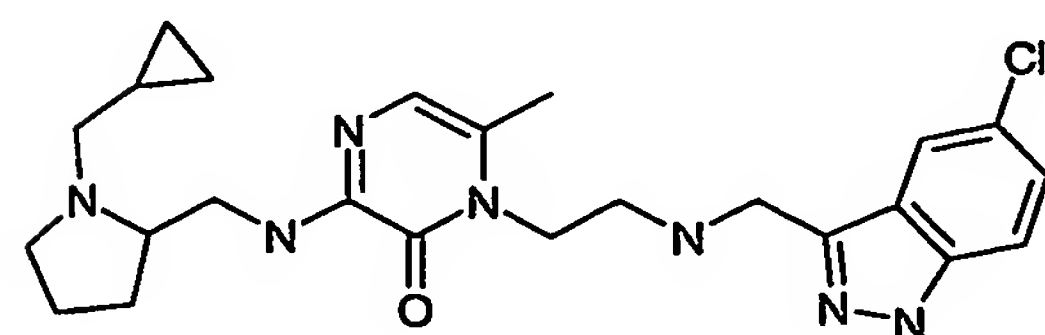
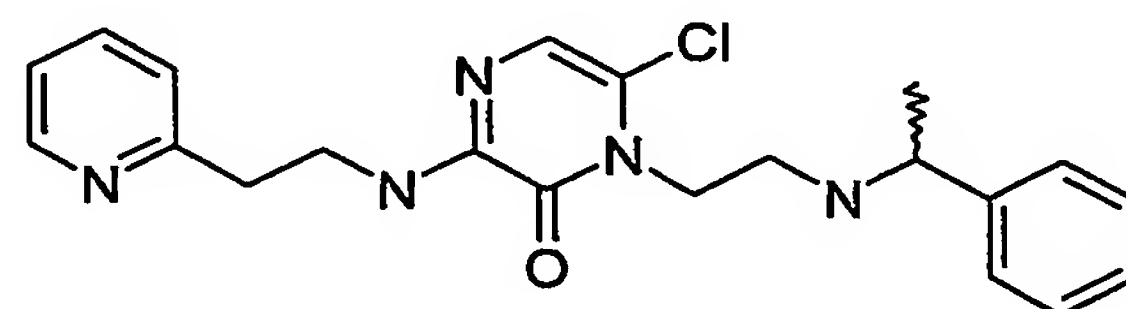
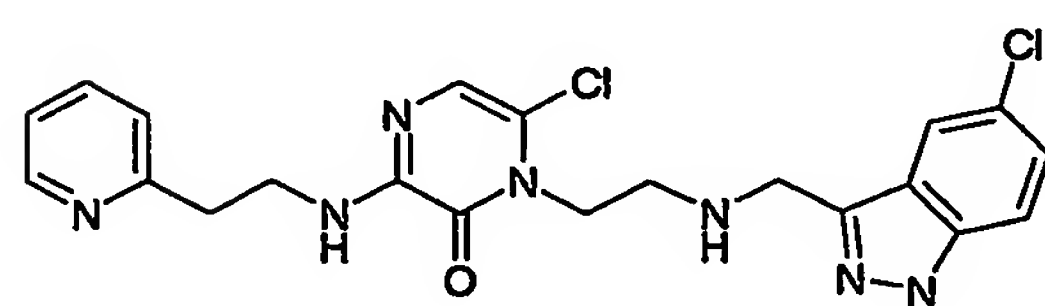
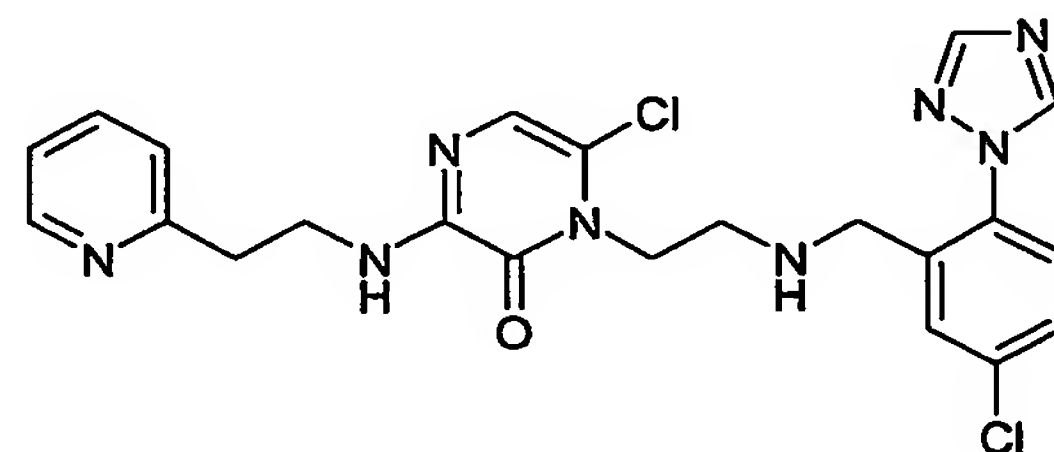
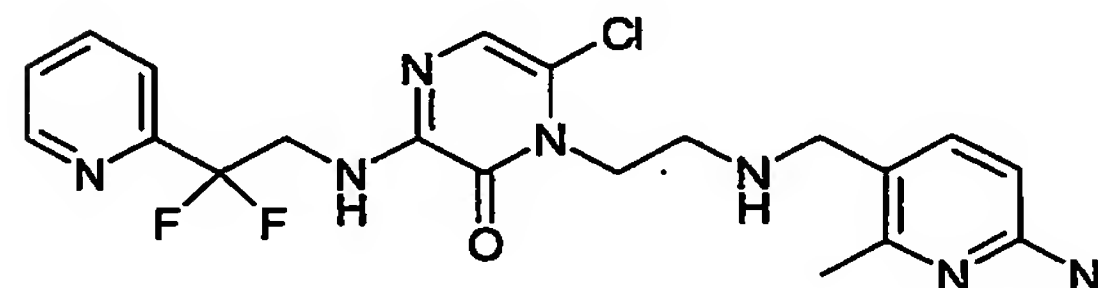
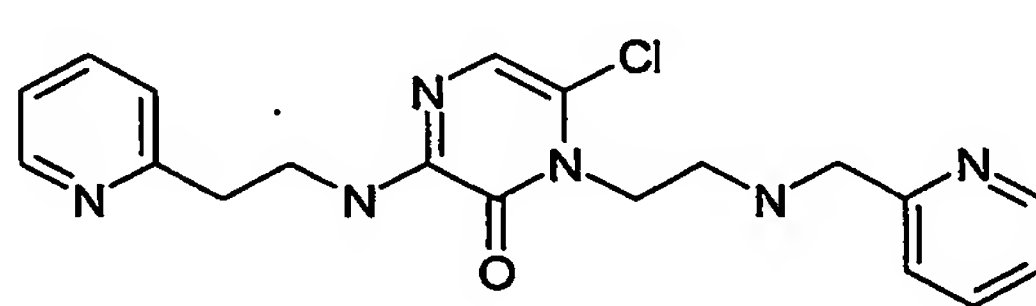
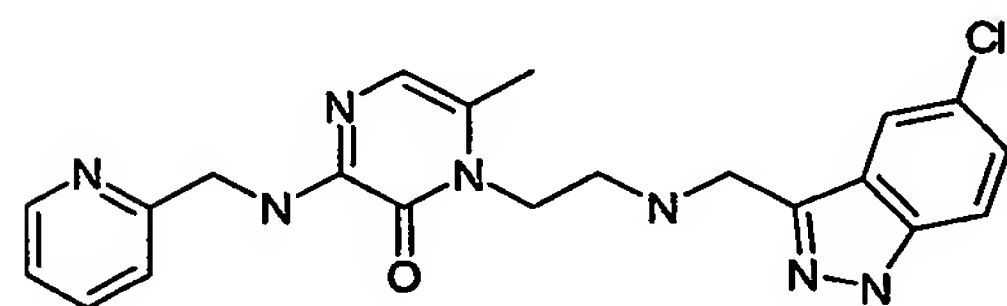
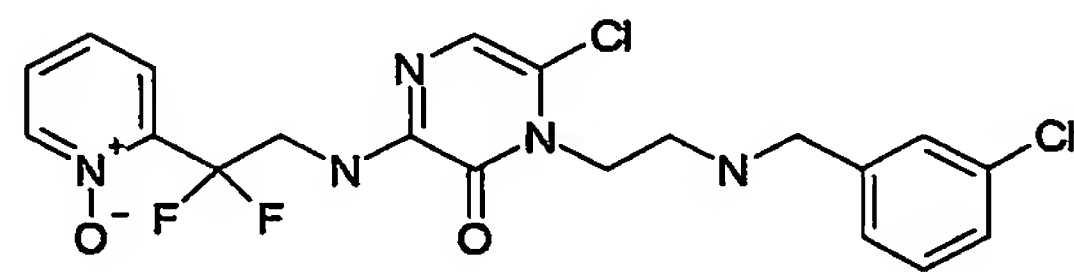
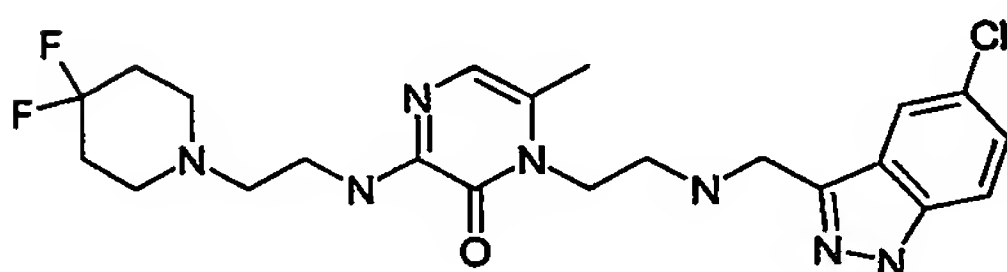
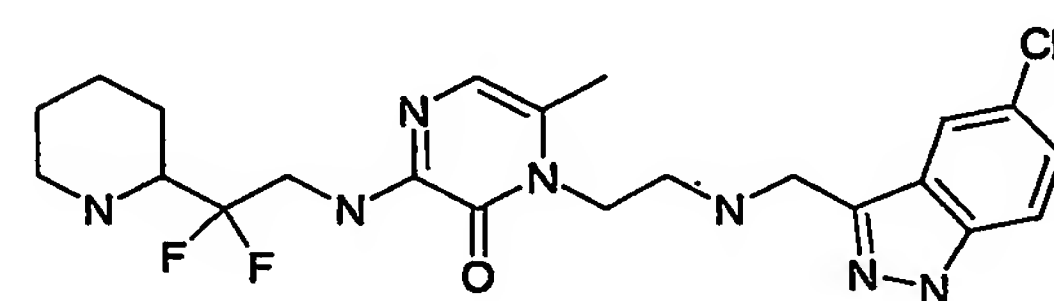
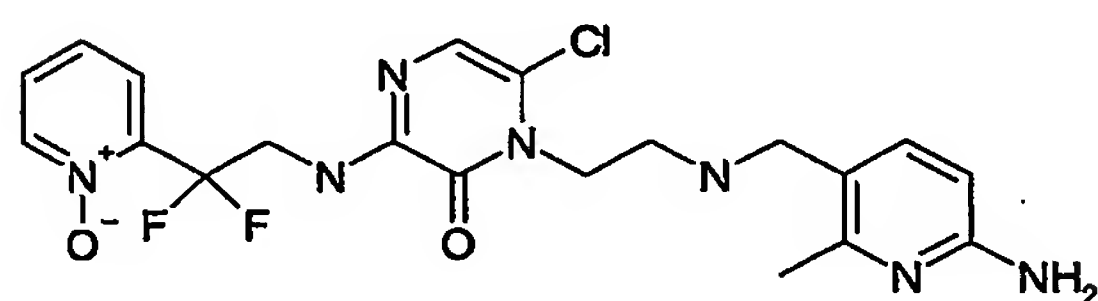
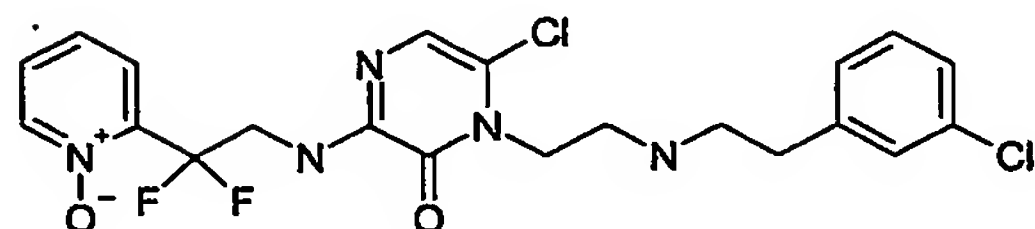
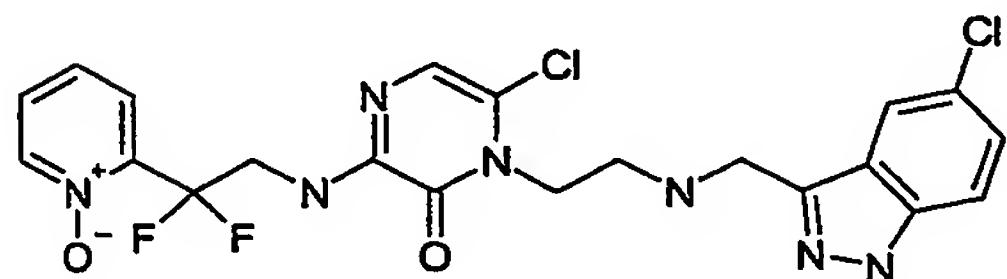
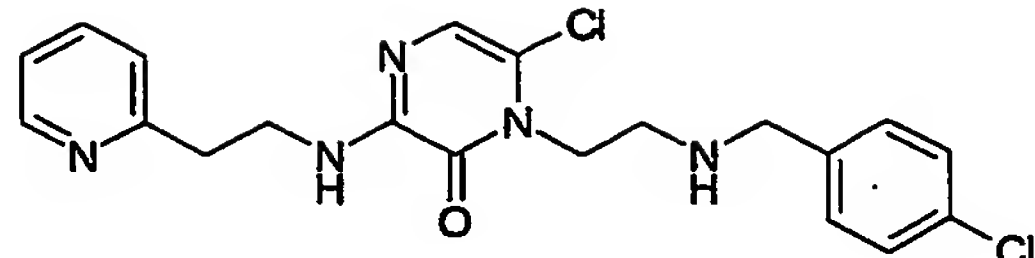
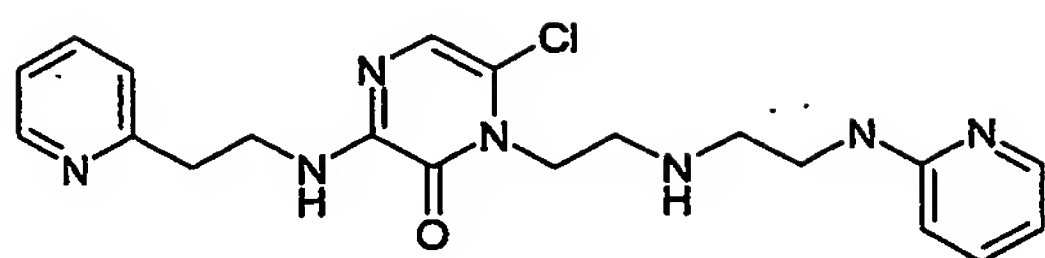
21. A compound according to claim 1 selected from the group consisting of:

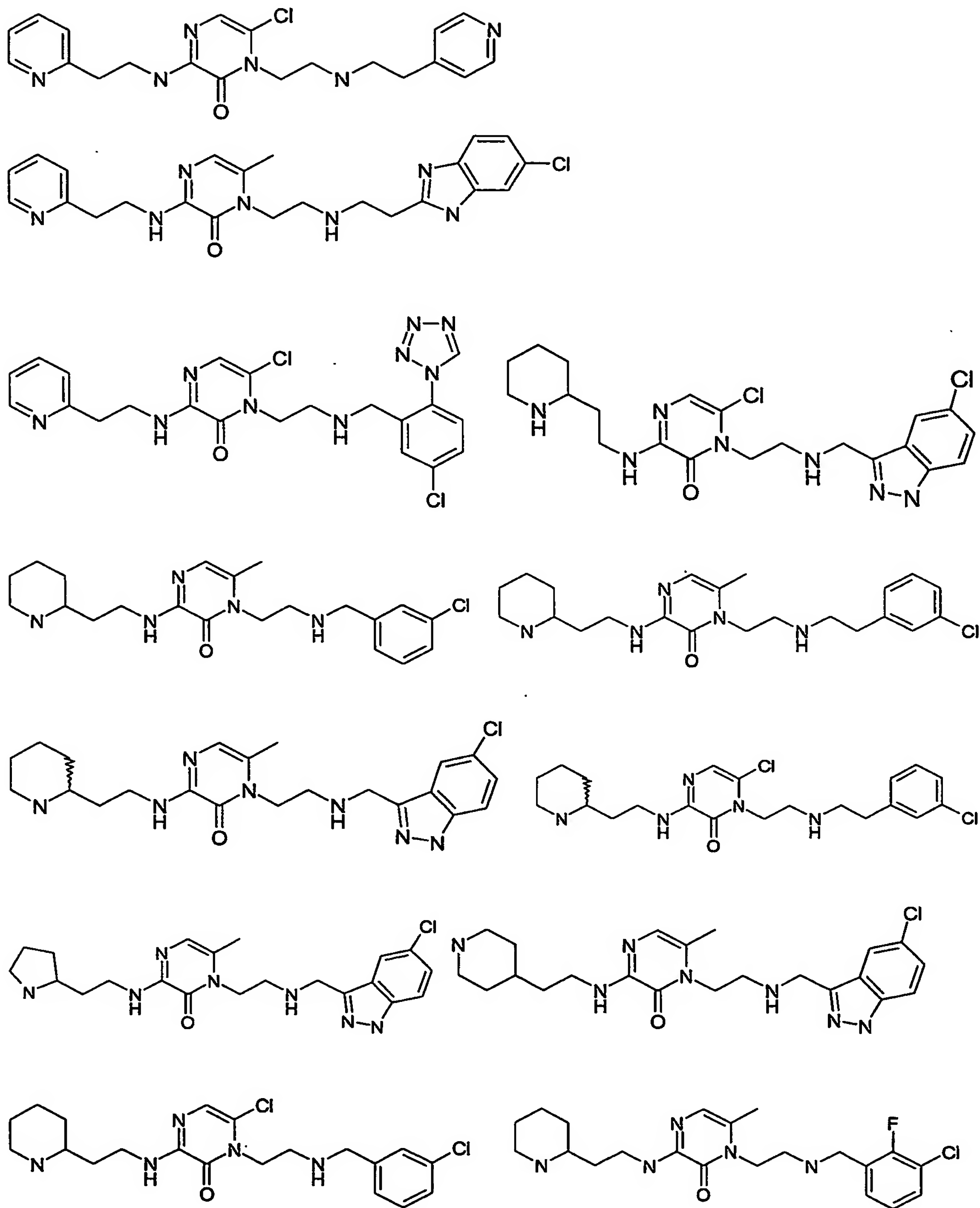


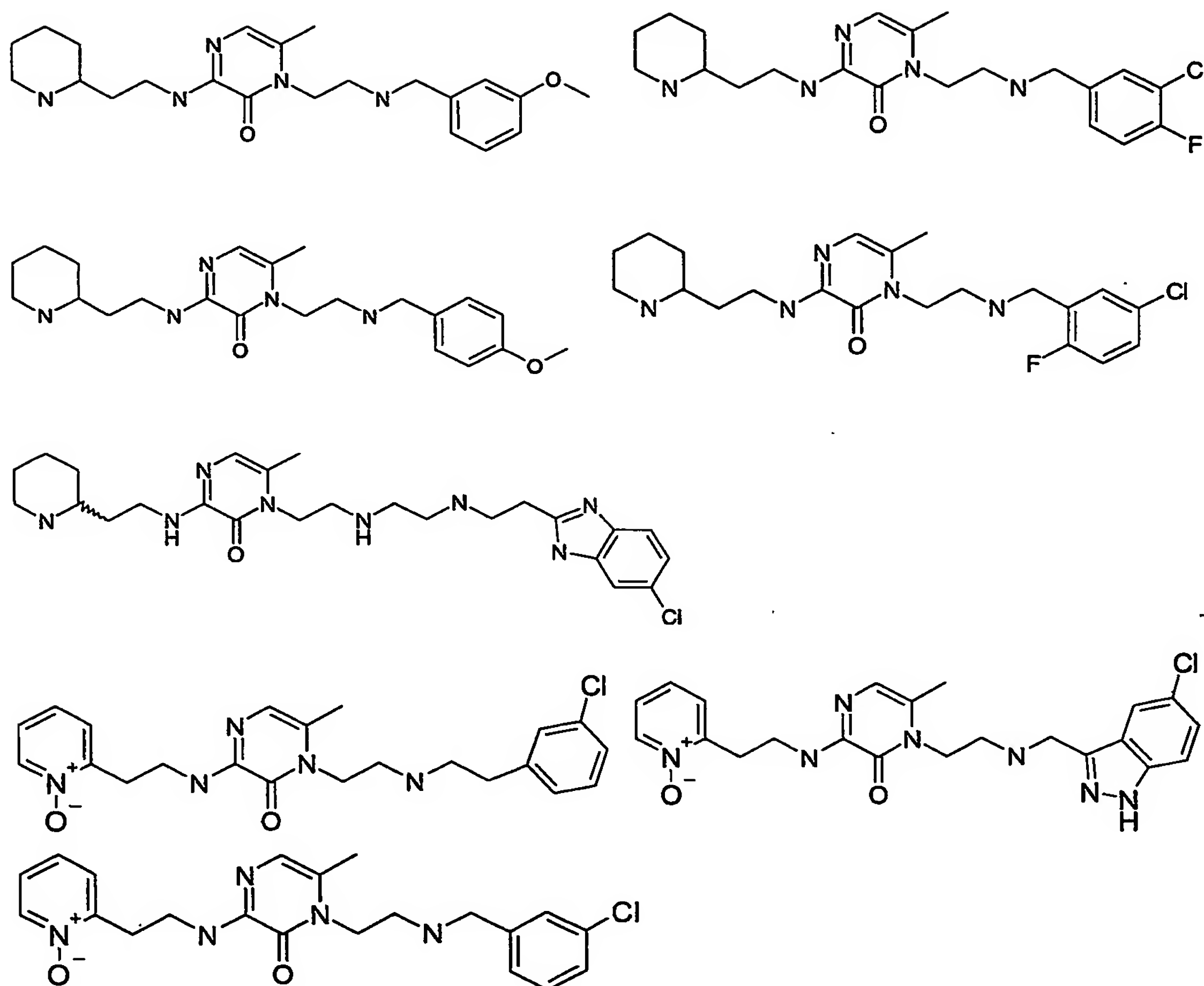












22. A prodrug of a compound according to any one of the claims 1 to 21.
23. A pharmaceutical composition comprising a compound or a mixture of compounds or a pharmaceutically acceptable salt thereof according to any one of the claims 1 to 21 together with a pharmaceutically acceptable carrier.
24. A pharmaceutical composition comprising a prodrug according to claim 22 or a mixture of prodrugs or prodrugs and compounds according to any one of the claims 1 to 21 or a pharmaceutically acceptable salt together with a pharmaceutically acceptable carrier.
25. A pharmaceutical composition according to claim 23 or 24, additionally comprising one or more known anticoagulants.

26. A compound or a pharmaceutically acceptable salt of any one of the claims 1 to 21 for use as a medicament.
27. A prodrug or a pharmaceutically acceptable salt of claim 22 for use as a medicament.
28. Use of a compound or a pharmaceutically acceptable salt of any of the claims 1 to 21 for the manufacture of a medicament for the treatment or prophylaxis of thromboembolism, thrombosis, arteriosclerosis, unstable angina, refractory angina, myocardial infarction, transient ischemic attacks, atrial fibrillation, thrombotic stroke, embolic stroke, deep vein thrombosis, disseminated intravascular coagulation, ocular build up of fibrin, and reocclusion or restenosis of recanalized vessels.
29. Use of a prodrug or a pharmaceutically acceptable salt of claim 22 for the manufacture of a medicament for the treatment or prophylaxis of thromboembolism, thrombosis, arteriosclerosis, unstable angina, refractory angina, myocardial infarction, transient ischemic attacks, atrial fibrillation, thrombotic stroke, embolic stroke, deep vein thrombosis, disseminated intravascular coagulation, ocular build up of fibrin, and reocclusion or restenosis of recanalized vessels.
30. Use of a compound according to any one of the claims 1 to 21 or a prodrug according to claim 22 as an anticoagulant or thrombin inhibitor.